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Signed Stephen Hordley

Dated 9 December 2004

Patents Form 1/77

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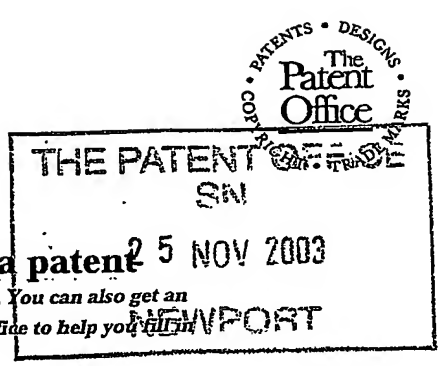

1/77

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P01/7700 0.00-0327331.5

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference 101120-1 GB

2. Patent application number *(The Patent Office will fill in this part)* 0327331.5

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number *(if you know it)* 7822448003

If the applicant is a corporate body, give the country/state of its incorporation Sweden

4. Title of the invention

THERAPEUTIC AGENTS

5. Name of your agent *(if you have one)* Thomas Kerr MILLER

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

AstraZeneca
Global Intellectual Property
PO Box 272
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4GR

Patents ADP number *(if you know it)* 8179707002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

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Continuation sheets of this form	
Description	25
Claim *(s)*	
Abstract	1
Drawing *(s)*	

SN

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Kevin Bill Date 24/11/03

Kevin Bill - Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom: Jennifer Bennett - 01625 230148

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THERAPEUTIC AGENTS

Field of invention

The present invention relates to certain compounds of formula I, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, to methods for their therapeutic use and to pharmaceutical compositions containing them.

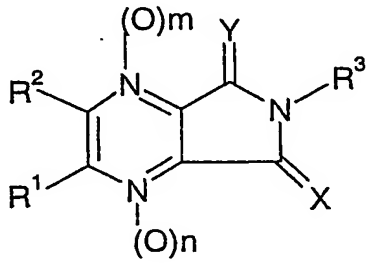
Background of the invention

It is known that certain CB_1 modulators (known as antagonists or inverse agonists) are useful in the treatment of obesity, psychiatric and neurological disorders (WO01/70700 and EP 656354). However, there is a need for CB_1 modulators with improved physicochemical properties and/or DMPK properties and/or pharmacodynamic properties.

2,3-Diphenyl- 5H-pyrrolo[3,4-b]pyrazine-5,7(6H)-dione is disclosed in Agricultural and Biological Chemistry (1981), 45(9), 2129-30 and in Journal of Polymer Science, Polymer Chemistry Edition (1971), 9(4), 1117-38.

Description of the invention

The invention relates to a compound of formula (I)



I

and pharmaceutically acceptable salts thereof, in which

R^1 and R^2 independently represent phenyl, thienyl, pyridyl, C_{1-10}alkyl, C_{1-10}alkoxy or C_{3-15}cycloalkyl ;

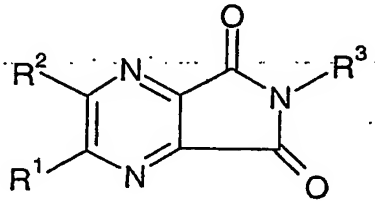
R^3 represents a C_{1-15}alkyl group, C_{3-15}cycloalkyl, a phenylC_{1-4}alkyl group, a heteroarylC_{1-4}alkyl group, or a group $R^4(CH_2)_n$- in which R^4 represents a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from nitrogen, oxygen or sulphur and n is 0, 1, 2, 3 or 4;

X and Y independently represent O or S;

m and n independently represent 0 or 1;

wherein each of R^1, R^2, R^3 and R^4 is optionally substituted by one, two or three groups represented by Z wherein Z represents a C_{1-6}alkyl group optionally substituted by one or more fluoro, a C_{1-6}alkoxy group optionally substituted by one or more fluoro, hydroxy, halo, trifluoromethylsulphonyl, benzyl, nitro, amino, mono or di C_{1-4}alkylamino, mono or di C_{1-3}alkylamido, C_{1-3}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl, sulphamoyl or acetyl.

A particular group of compounds of formula I is represented by formula IA



IA

in which R^1, R^2 and R^3 are as previously defined.

It will be understood that where a substituent Z is present in more than one group that these substituents are independently selected and may be the same or different.

The term C_{3-15}cycloalkyl includes monocyclic, bicyclic, tricyclic and spiro systems for example, cyclopentyl, cyclohexyl and adamantyl.

The term heteroaryl means an aromatic 5- , 6-, or 7-membered monocyclic ring or a 9- or 10-membered bicyclic ring, with up to five ring heteroatoms selected from oxygen,

nitrogen and sulfur. Suitable aromatic heteroaryl groups include, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl. Preferably furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, oxazolyl thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazenyl and more preferably pyrrolyl, thienyl, imidazolyl, oxazolyl or pyridyl.

Suitable saturated or partially unsaturated 5 to 8 membered heterocyclic groups containing one or more heteroatoms selected from nitrogen, oxygen or sulphur include, for example oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, 2,3-dihydro-1,3-thiazolyl, 1,3-thiazolidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 1-oxotetrahydrothienyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, piperidinyl or piperazinyl, more preferably tetrahydrofuran-3-yl, tetrahydropyran-4-yl, pyrrolidin-3-yl, morpholino, piperidino, piperidin-4-yl or piperazin-1-yl.

Particularly Z represents halo, trifluoromethyl, trifluoromethylthio, difluoromethoxy or trifluoromethoxy.

Further values of R^1, R^2, R^3, and R^4 in compounds of formula I and compounds of formula IA now follow. It will be understood that such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

R^1 and R^2 independently represent phenyl optionally substituted independently by one or two halo. Particularly R^1 and R^2 are identical. More particularly R^1 and R^2 each represent 4-chlorophenyl.

R^3 represents a phenylC_{1-4}alkyl, pyridylC_{1-4}alkyl, a C_{1-6}alkyl group, piperidino, morpholino, pyrrolidino wherein the phenyl ring is optionally substituted by halo and the pyridyl ring is optionally substituted by one or more of the following :halo, a C_{1-6}alkyl group (optionally substituted by one or more fluoro for example trifluoromethyl), or a C_{1-6}alkoxy group (optionally substituted by one or more fluoro for example difluoromethoxy or trifluoromethoxy). Particularly R^3 represents benzyl, halobenzyl, pyridylmethyl, piperidino or a C_{3-4}alkyl group. More particularly R^3 represents 4-fluorobenzyl, 4-pyridylmethyl, piperidino or *tert*-butyl.

X and Y both present O.

m and n are both 0.

In one group of compounds of formula I R^1 and R^2 independently represent phenyl optionally substituted independently by one or two chloro, R^3 represents benzyl, halobenzyl, pyridylmethyl, piperidino or a C_{3-4}alkyl group, X and Y are both O and m and n are both 0.

"Pharmaceutically acceptable salt", where such salts are possible, includes both pharmaceutically acceptable acid and base addition salts. A suitable pharmaceutically acceptable salt of a compound of Formula I is, for example, an acid-addition salt of a compound of Formula I which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a sodium, calcium or magnesium salt, or an ammonium salt,or a salt with an organic base such as

methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof and solvates thereof such as for instance hydrates. Isomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention. All tautomers, where possible, are included within the scope of the invention.

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "alkyl" denotes either a straight or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl and t-butyl . Preferred alkyl groups are methyl, ethyl, propyl, isopropyl and tertiary butyl.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

Unless otherwise stated or indicated, the term "halogen" shall mean fluorine, chlorine, bromine or iodine.

Specific compounds of the invention are one or more of the following:

2,3-bis(4-chlorophenyl)-6-(4-fluorobenzyl)-5H-pyrrolo[3,4-b]pyrazine-5,7(6H)-dione;

2,3-bis(4-chlorophenyl)-6-(pyridin-4-ylmethyl)-5*H*-pyrrolo[3,4-*b*]pyrazine-5,7(6*H*)-dione;

2,3-bis(4-chlorophenyl)-6-piperidin-1-yl-5*H*-pyrrolo[3,4-*b*]pyrazine-5,7(6*H*)-dione; or

6-*tert*-butyl-2,3-bis(4-chlorophenyl)-5*H*-pyrrolo[3,4-*b*]pyrazine-5,7(6*H*)-dione

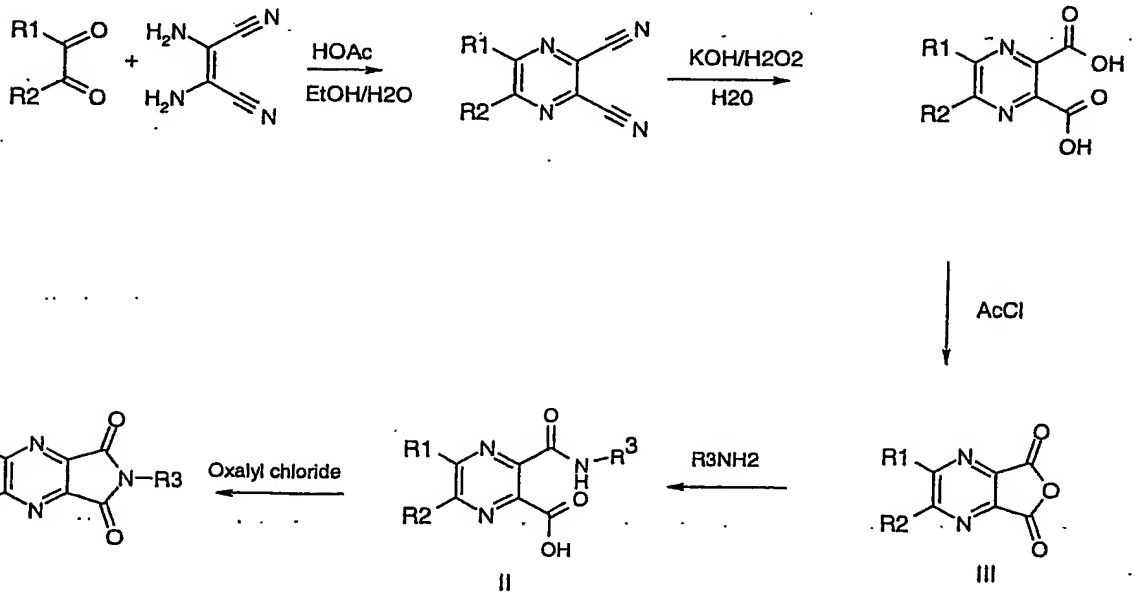
as well as pharmaceutically acceptable salts thereof.

Methods of preparation

The compounds of the invention may be prepared as outlined below according to any of the following methods. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

Compounds of formula I in which m and n are each 0 and X and Y are both O are prepared by reacting a compound of formula II with a dehydrating agent for example oxalyl chloride optionally in the presence of a solvent for the compound of formula II at a temperature in the range of 0-100°C.

Synthetic Scheme



Compounds of formula I in which either X or Y or both X and Y are S may be prepared by reacting a compound of formula I in which X and Y are both O with an appropriate molar amount of Lawesson's reagent by methods known to those skilled in the art.

Compounds of formula I in which either of n and m is 1 or both are 1 may be prepared by oxidising a compound of formula I in which n and m are both 0 with an appropriate molar quantity of oxidising agent for example a peroxide e.g.hydrogen peroxide or sulphuric peroxide.

Certain compounds of formula II and III are believed to be novel and form part of the present invention.

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient or a pharmaceutically acceptable addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-1 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders(e.g. Multiple Sclerosis), Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, septic shock and diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea). The compounds are also potentially useful as agents in treatment of extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms. The compounds may also eliminate the increase in weight which normally accompanies the cessation of smoking.

In another aspect the present invention provides a compound of formula I as previously defined for use as a medicament.

In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia, bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease,

immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms.

In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders such as schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders like ADHD, epilepsy, and related conditions, neurological disorders such as dementia, neurological disorders (e.g. Multiple Sclerosis), Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems (e.g. diarrhea), and extended abuse, addiction and/or relapse indications, e.g. treating drug (nicotine, ethanol, cocaine, opiates, etc) dependence and/or treating drug (nicotine, ethanol, cocaine, opiates, etc) withdrawal symptoms comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

The compounds of the present invention are particulary suitable for the treatment of obesity, e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of obesity such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and atherosclerosis. For example, a compound of the present invention may be used in combination with a compound that affects thermogenesis, lipolysis, fat absorption, satiety, or gut motility. The compounds of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compounds of the

invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of obesity and its associated complications the metabolic syndrome and type 2 diabetes, these include biguanide drugs, insulin (synthetic insulin analogues) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors).

In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt thereof may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art.

In addition the combination of the invention may be used in conjunction with a sulfonylurea. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor). The present invention also includes a compound of the present invention in combination with a bile acid binding resin.

The present invention also includes a compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor;

a cholesterol absorption antagonist;

a MTP (microsomal transfer protein) inhibitor ;

a nicotinic acid derivative, including slow release and combination products;

a phytosterol compound ;

probucol;

an anti-coagulant;

an omega-3 fatty acid ;

another anti-obesity compound;

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic, or a vasodilator;

a Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

an SSRI;

a serotonin antagonist;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Therefore in an additional feature of the invention, there is provided a method for for the treatment of obesity and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in

simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula I, or a pharmaceutically acceptable salt thereof, in a first unit dosage form;

b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of formula I, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of obesity and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Furthermore, a compound of the invention may also be combined with therapeutic agents that are useful in the treatment of disorders or conditions associated with obesity (such as

type II diabetes, metabolic syndrome, dyslipidemia, impaired glucose tolerance, hypertension, coronary heart disease, non-alcoholic steatorheic hepatitis, osteoarthritis and some cancers) and psychiatric and neurological conditions.

Pharmacological Activity

Compounds of the present invention are active against the receptor product of the CB1 gene. The affinity of the compounds of the invention for central cannabinoid receptors is demonstrable in methods described in Devane et al , Molecular Pharmacology, 1988, 34,605 or those described in WO01/70700 or EP 656354. Alternatively the assay may be performed as follows.

10μg of membranes prepared from cells stably transfected with the CB1 gene were suspended in 200μl of 100mM NaCl, 5mM $MgCl_2$, 1mM EDTA, 50mM HEPES (pH 7.4), 1mM DTT, 0.1% BSA and 100μM GDP. To this was added an EC80 concentration of agonist (CP55940), the required concentration of test compound and 0.1μCi [^{35}S]-GTPγS. The reaction was allowed to proceed at 30°C for 45 min. Samples were then transferred on to GF/B filters using a cell harvester and washed with wash buffer (50mM Tris (pH 7.4), 5mM $MgCl_2$, 50mM NaCl). Filters were then covered with scintilant and counted for the amount of [^{35}S]-GTPγS retained by the filter.

Activity is measured in the absence of all ligands (minimum activity) or in the presence of an EC80 concentration of CP55940 (maximum activity). These activities are set as 0% and 100% activity respectively. At various concentrations of novel ligand, activity is calculated as a percentage of the maximum activity and plotted. The data are fitted using the equation y=A+((B-A)/1+((C/x) ÙD)) and the IC50 value determined as the concentration required to give half maximal inhibition of GTPγS binding under the conditions used.

The compounds of the present invention are active at the CB1 receptor (IC50 <1 micromolar). Most preferred compounds have IC50 <200 nanomolar.

The compounds of the invention are believed to be selective CB1 antagonists.

Examples

Abbreviations

DCM - dichloromethane

DMF - dimethylformamide

DMAP - 4-dimethylaminopyridine

EDC - 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

TEA – triethylamine

TFA – trifluoroacetic acid

DMSO-dimethyl sulfoxide

DEA - Diethylamine

PCC - Pyridinium chlorochromate

PyBOP - benzotriazol-1-yl-oxytri-pyrrolidinophosphonium hexafluorophosphate

HBTU - *O*-Benzotriazol-1-yl-*N,N,N´,N´*-tetramethyluronium Hexafluorophosphate

DAST-(diethyl amino)sulphur trifluoride

DIEA - *N,N*-diisopropylethylamine

t	triplet
s	singlet
d	doublet
q	quartet
qvint	quintet
m	multiplet
br	broad
bs	broad singlet
dm	doublet of multiplet
bt	broad triplet
dd	doublet of doublet

General Experimental Procedures

Mass spectra were recorded on either a Micromass ZQ single quadrupole or a Micromass LCZ single quadrupole mass spectrometer both equipped with a pneumatically assisted electrospray interface (LC-MS). ^{1}H NMR measurements were performed on either a

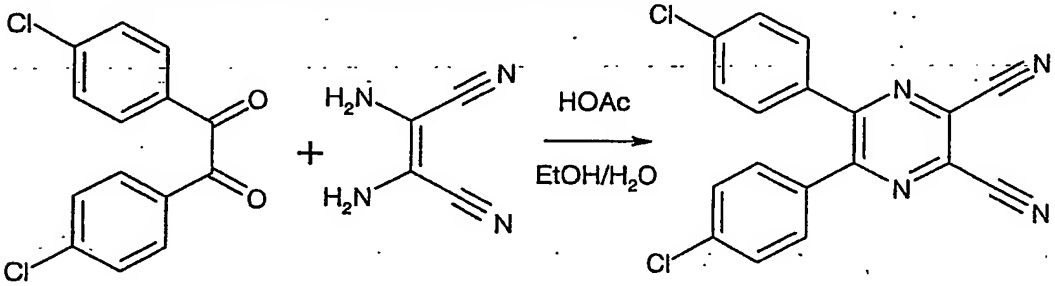
Varian Mercury 300 or a Varian Inova 500, operating at ^1H frequencies of 300 and 500 MHz respectively. Chemical shifts are given in ppm with $CDCl_3$ as internal standard. $CDCl_3$ is used as the solvent for NMR unless otherwise stated. Purification was performed on a semipreparative HPLC with a mass triggered fraction collector, Shimadzu QP 8000 single quadrupole mass spectrometer equipped with 19 x 100 mm C8 column. The mobile phase used was, if nothing else is stated, acetonitrile and buffer (0.1 M NH_4Ac:acetonitrile 95:5).

For isolation of isomers, a Kromasil CN E9344 (250 x 20 mm i.d.) column was used. Heptane:ethyl acetate:DEA 95:5:0.1 was used as mobile phase (1 ml/min). Fraction collection was guided using a UV-detector (330 nm).

Examples of the Invention

Example 1

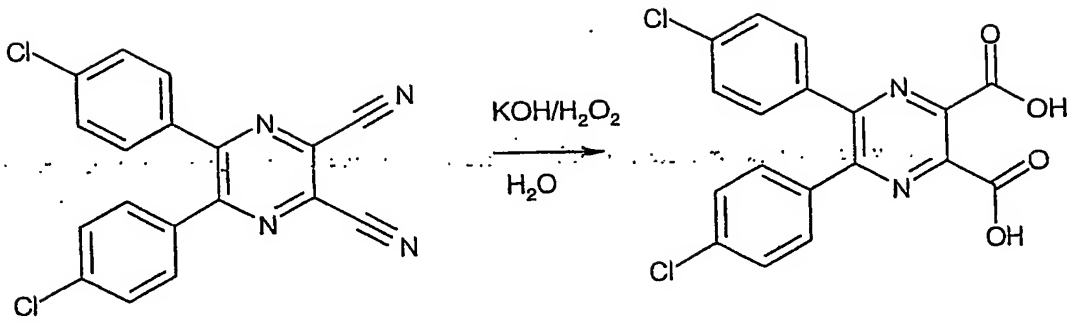
Step A 5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarbonitrile



A mixture of 1,2-bis(4-chlorophenyl)ethane-1,2-dione, (20 g, 71.65 mmol), diaminomaleonitrile (8.5 g, 78.82 mmol) and acetic acid (6 ml) in ethanol (140 ml) and water (93 ml) was heated at 75 °C overnight. The reaction mixture was cooled, and water was added. The precipitate was filtered and washed with ethanol and then ether. The crude product was dissolved in DCM and treated with activated charcoal, then filtered through celite. The solid was recrystallized from DCM/ethanol to give the title compound (17.3 g, 69%) as a solid.

^1H NMR (400 MHz) δ 7.49 (d, 4H), 7.38 (d, 4H).

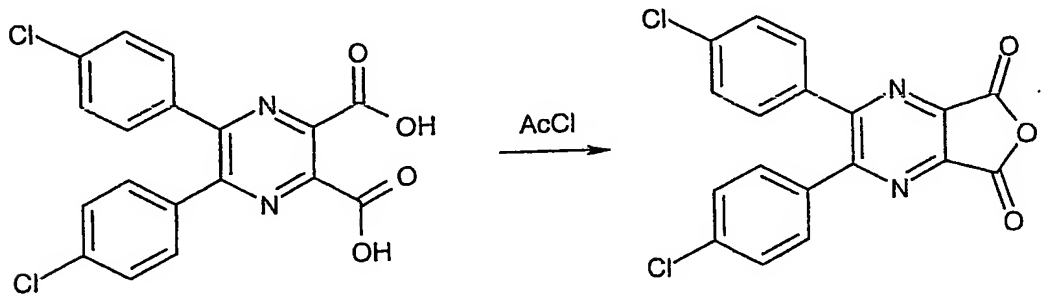
Step B 5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarboxylic acid



To a suspension of 5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarbonitrile, Example 1, Step A (16.3 g, 46.28 mmol) and KOH (26 g, 463 mmol) in water (84 ml) was added hydrogen peroxide (35%, 19 ml) followed by a few drops of nonanol to reduce foaming. The reaction mixture was boiled under reflux for 2h, cooled and washed with ether and acidified to pH 4 with 2M HCl. The precipitate was filtered, washed with water and dried under reduced pressure to give the crude product which was esterified by refluxing in hydrogen chloride/methanol (100 ml) followed by HPLC purification, giving 12.85 g of the methyl ester. The resulting methyl ester in acetonitrile (140 ml) and water (90 ml) was treated with lithium hydroxide (2.95 g, 0.123 mmol) at ambient temperature for 1.5 h. The acetonitrile was removed under reduced pressure and the aqueous solution was washed with diethyl ether. Acidification with hydrochloric acid (2M) gave the title compound (11.8 g, 66% mmol) as a pale yellow solid which was isolated by filtration.

^{1}H NMR (400 MHz) δ 7.51 (d, 4H), 7.41 (d, 4H). MS *m/z* 389, 391 $(M+H)^+$.

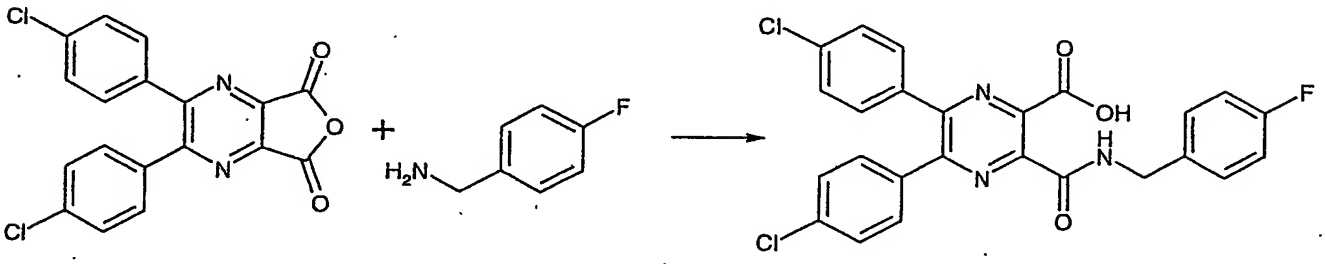
Step C 2,3-bis(4-chlorophenyl)furo[3,4-*b*]pyrazine-5,7-dione



A mixture of 5,6-bis(4-chlorophenyl)pyrazine-2,3-dicarboxylic acid, Example 1, Step B (6.7 g, 17.30 mmol) and acetyl chloride (20 ml) was boiled under reflux overnight. The excess of acetyl chloride was removed under reduced pressure to give the title compound (6.2 g, 97%) as a solid.

^{1}H NMR (400 MHz) δ 7.51 (d, 4H), 7.41 (d, 4H).

Step D 5,6-bis(4-chlorophenyl)-3-{[(4-fluorobenzyl)amino]carbonyl}pyrazine-2-carboxylic acid:

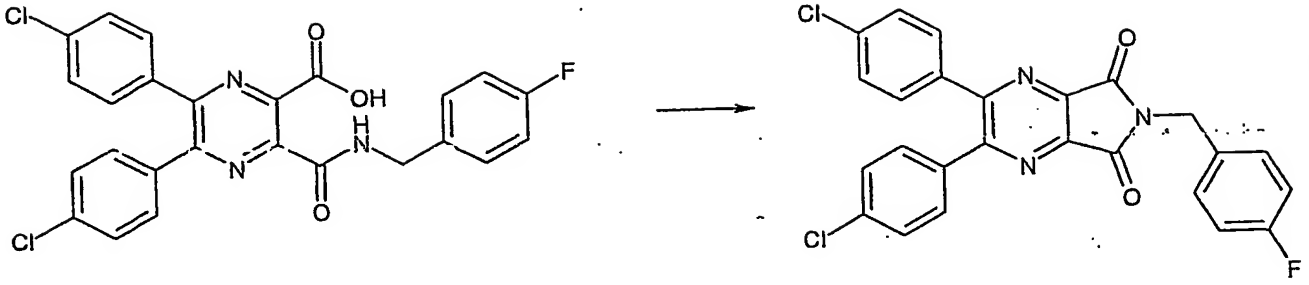


(4-Fluorobenzyl)amine (202 mg, 1.61 mmol) was mixed with 2,3-bis(4-chlorophenyl)furo[3,4-*b*]pyrazine-5,7-dione Ex. 1, Step C (544 mg, 1.47 mmol) in acetonitrile (10 ml). The reaction mixture was left at room temperature for 60 h. Evaporation followed by purification by HPLC gave the pure compound (700 mg, 96%).

^{1}H NMR (500 MHz, CD_3OD) δ 7.55-7.46 (m, 4H), 7.46-7.39 (m, 2H), 7.39-7.34 (m, 4H), 7.08-7.01 (m, 2H) 4.60 (s, 2H).

MS *m/z* calcd for $[C_{25}H_{17}Cl_2N_3O_3F]H^+$ 496.0631, found 496.0643 $(M+H)^+$

Step E 2,3-bis(4-chlorophenyl)-6-(4-fluorobenzyl)-5H-pyrrolo[3,4-b]pyrazine-5,7(6H)-dione :



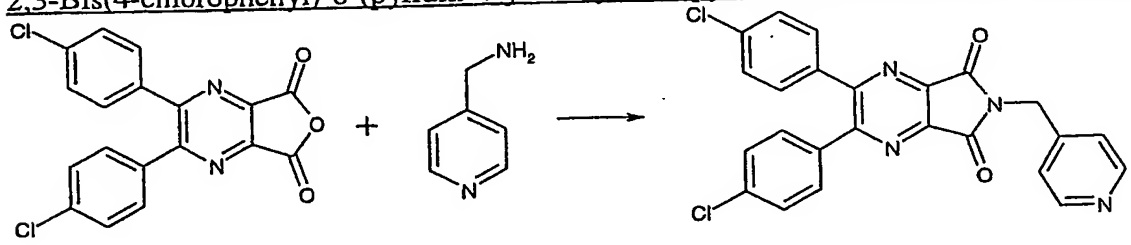
5,6-Bis(4-chlorophenyl)-3-{[(4-fluorobenzyl)amino]carbonyl}pyrazine-2-carboxylic acid, Ex.1, Step D (220 mg, 0.443 mmol) was dissolved in methylene chloride (5 ml). DMF (20 microlitres) was added and then oxalyl chloride (1 ml). After 1 hour at room temperature the solvent was removed in vacuo and the residue was purified by preparative HPLC to give the title compound (156 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.42 (m, 6H), 7.36-7.30 (d, 4H), 7.05-6.96 ("t", 2H), 4.95 (s, 2H).

MS *m/z* calcd for $[C_{25}H_{14}Cl_2FN_3O_2]H^+$ 478.0528, found 478.0559 $(M+H)^+$.

Example 2

2,3-Bis(4-chlorophenyl)-6-(pyridin-4-ylmethyl)-5*H*-pyrrolo[3,4-*b*]pyrazine-5,7(6*H*)-dione



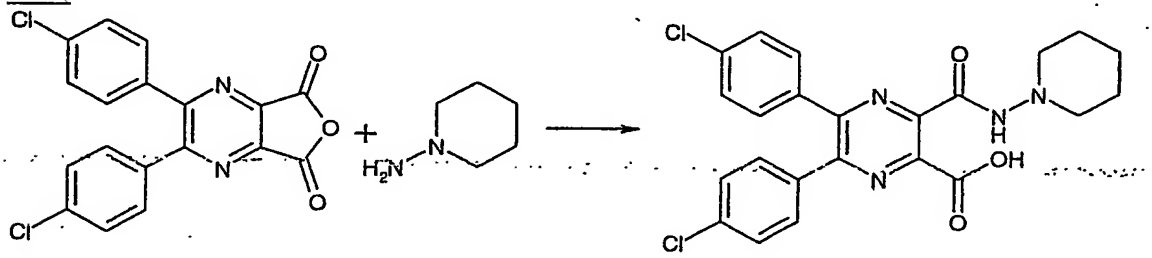
2,3-Bis(4-chlorophenyl)furo[3,4-*b*]pyrazine-5,7-dione, EX1, Step C (214 mg, 0.58 mmol) was dissolved in methylene chloride (3 ml) followed by (pyridin-4-ylmethyl)amine (62 mg, 0.58 mmol). After 5 days at room temperature, DMF (20 microlitres) and thionyl chloride (1 ml) were added. The solvent was removed in vacuo after 1 hour and the residue was purified by preparative HPLC to give the title compound (104 mg, 39%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (broad s, 2H), 7.45 (d, 4H), 7.35-7.29 (m, 6H), 4.97 (s, 2H).

MS *m/z* calcd for $[C_{24}H_{14}Cl_2N_4O_2]H^+$ 461.0572, found 461.0585 $(M+H)^+$

Example 3

StepA 5,6-bis(4-chlorophenyl)-3-[(piperidin-1-ylamino)carbonyl]pyrazine-2-carboxylic acid:

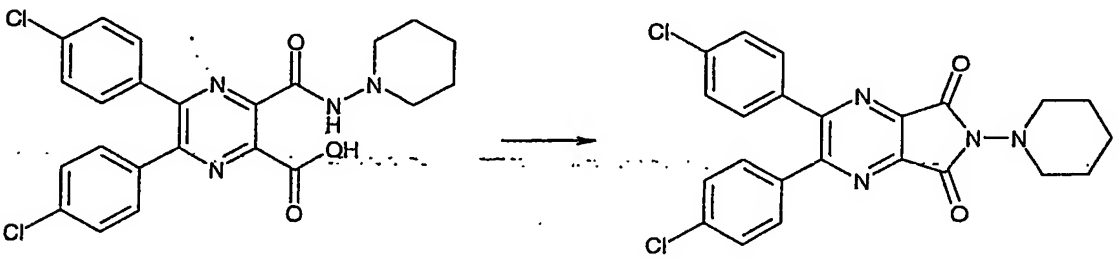


A solution of piperidin-1-amine (292 mg, 2.91 mmol) in acetonitrile (10 ml) was added to a solution of 2,3-bis(4-chlorophenyl)furo[3,4-*b*]pyrazine-5,7-dione, Ex1, Step C (1.03 g, 2.78 mmol) in acetonitrile (10 ml). After 2 hours the solvent was removed in vacuo and the title compound could be isolated by crystallization from acetonitrile. The yield was 807 mg (62%).

^{1}H NMR (400 MHz) δ 7.55 (d, 2H), 7.46 (d, 2H), 7.37 (d, 2H), 7.31 (d, 2H), 3.05-2.97 (m, 4H), 1.84-1.77 (m, 4H), 1.54-1.46 (m, 2H).

MS *m/z* calcd for $[C_{23}H_{21}Cl_2N_4O_3]H^+$ 471.0991, found 471.0994 $(M+H)^+$.

Step B2,3-bis(4-chlorophenyl)-6-piperidin-1-yl-5*H*-pyrrolo[3,4-*b*]pyrazine-5,7(6*H*)-dione:

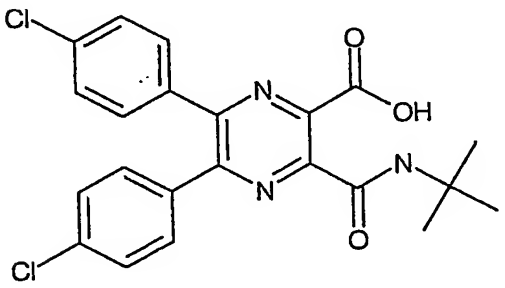


Oxalyl chloride (0.4 ml) was added to 5,6-bis(4-chlorophenyl)-3-[(piperidin-1-ylamino)carbonyl]pyrazine-2-carboxylic acid (229 mg, 0.486 mmol) in methylene chloride (10 ml). After 10 minutes water was added and then sodium carbonate solution.

The organic phase was washed with water and the solvent was evaporated. The product was isolated by crystallisation from methylene chloride/hexane (92 mg, 42%).
^{1}H NMR (400 MHz) δ 7.47 (d, 4H), 7.34 (d, 4H), 3.41-3.36 (m, 4H), 1.84-1.76 (m, 4H), 1.60-1.50 (m, 2H).
MS *m/z* calcd for $[C_{23}H_{18}Cl_2N_4O_2]H^+$ 453.0918, found 453.0885 $(M+H)^+$.

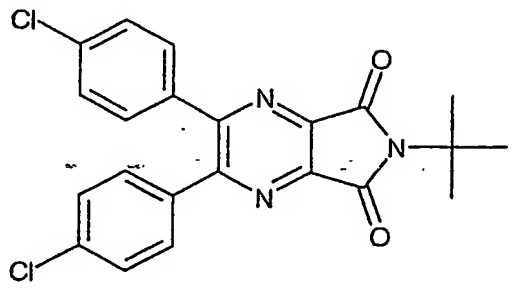
Example 4

STEP A 3-[(*tert*-butylamino)carbonyl]-5,6-bis(4-chlorophenyl)pyrazine-2-carboxylic acid



To a solution of 2,3-bis(4-chlorophenyl)furo[3,4-*b*]pyrazine-5,7-dione, Ex.1, stepC (500 mg, 1.35 mmol) in acetonitrile (10 ml) was added *tert*-butylamine (99 mg, 1.35 mmol). The reaction mixture was stirred in room temperature for 1h 15min to give the subtitle compound. ^{1}H NMR (400 MHz) δ 7.46-7.41 (m, 4H), 7.38-7.34 (m, 4H), 1.41 (s, 9H).
MS *m/z* 444 $(M+H)^+$.

Step B 6-*tert*-butyl-2,3-bis(4-chlorophenyl)-5*H*-pyrrolo[3,4-*b*]pyrazine-5,7(6*H*)-dione

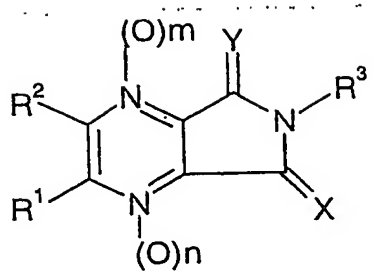


To a solution of 3-[(*tert*-butylamino)carbonyl]-5,6-bis(4-chlorophenyl)pyrazine-2-carboxylic, Ex. 4, Step A (100 mg, 0.23mmol) in methylene chloride (5 ml) were added oxalyl chloride (2.5 ml) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred in room temperature for 2hours. The mixture was then filtered through silica and preparatory HPLC gave the title compound as a solid. ^{1}H NMR (400 MHz) δ 7.45 (d, 4H), 7.32 (d, 4H), 1.75 (s, 9H).

MS *m/z* 426 $(M+H)^+$.

Claims

1. A compound of formula (I)



I

and pharmaceutically acceptable salts thereof, in which

R^1 and R^2 independently represent phenyl, thienyl, pyridyl, C_{1-10}alkyl, C_{1-10}alkoxy or C_{3-15}cycloalkyl ;

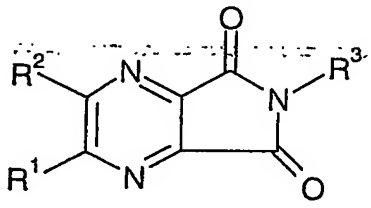
R^3 represents a C_{1-15}alkyl group, C_{3-15}cycloalkyl, a phenylC_{1-4}alkyl group, a heteroarylC_{1-4}alkyl group, or a group $R^4(CH_2)_n$- in which R^4 represents a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from nitrogen, oxygen or sulphur and n is 0, 1, 2, 3 or 4;

X and Y independently represent O or S;

m and n independently represent 0 or 1;

wherein each of R^1, R^2, R^3 and R^4 is optionally substituted by one, two or three groups represented by Z wherein Z represents a C_{1-6}alkyl group optionally substituted by one or more fluoro, a C_{1-6}alkoxy group optionally substituted by one or more fluoro, hydroxy, halo, trifluoromethylsulphonyl, benzyl, nitro, amino, mono or di C_{1-4}alkylamino, mono or di C_{1-3}alkylamido, C_{1-3}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl, sulphamoyl or acetyl.

2. A compound of formula (IA)



IA

and pharmaceutically acceptable salts thereof, in which

R^1 and R^2 independently represent phenyl, thienyl, pyridyl, C_{1-10}alkyl, C_{1-10}alkoxy or C_{3-15}cycloalkyl ;

R^3 represents a C_{1-15}alkyl group, C_{3-15}cycloalkyl, a phenylC_{1-4}alkyl group, a heteroarylC_{1-4}alkyl group, or a group $R^4(CH_2)_n$- in which R^4 represents a saturated or partially unsaturated 5 to 8 membered heterocyclic group containing one or more heteroatoms selected from nitrogen, oxygen or sulphur and n is 0, 1, 2, 3 or 4;

X and Y independently represent O or S;

m and n independently represent 0 or 1;

wherein each of R^1, R^2, R^3 and R^4 is optionally substituted by one, two or three groups represented by Z wherein Z represents a C_{1-6}alkyl group optionally substituted by one or more fluoro, a C_{1-6}alkoxy group optionally substituted by one or more fluoro, hydroxy, halo, trifluoromethylsulphonyl, benzyl, nitro, amino, mono or di C_{1-4}alkylamino, mono or di C_{1-3}alkylamido, C_{1-3}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carboxy, cyano, carbamoyl, mono or di C_{1-3}alkyl carbamoyl, sulphamoyl or acetyl.

3. A compound of formula I as claimed in either claim 1 or claim 2 for use as a medicament.

4. A pharmaceutical formulation comprising a compound of formula I according either claim 1 or claim 2 and a pharmaceutically acceptable adjuvant, diluent or carrier.

6. Use of a compound of formula I according to either claim 1 or claim 2 in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, and neurological disorders such as dementia, neurological disorders, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal systems, and extended abuse, addiction and/or relapse indications.

7. A method of treating obesity, psychiatric disorders, psychotic disorders, schizophrenia and bipolar disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, obsessive-compulsive disorders, anorexia, bulimia, attention disorders, epilepsy, and related conditions, neurological disorders, neurological disorders , Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease, immune, cardiovascular, reproductive and endocrine disorders, septic shock, diseases related to the respiratory and gastrointestinal system, and extended abuse, addiction and/or relapse indications, comprising administering a pharmacologically effective amount of a compound of formula I according to either claim 1 or claim 2 to a patient in need thereof.

8. A compound as defined in either claim 1 or claim 2 for use in the treatment of obesity.

ABSTRACT

The present invention relates to compounds of formula I and processes for preparing such compounds, their use in the treatment of obesity, psychiatric and neurological disorders, to methods for their therapeutic use and to pharmaceutical compositions containing them.